संत्यमेव जयते

INTELLECTUAL PROPERTY INDIA

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY,
PATENT OFFICE, DELHI BRANCH,
W - 5, WEST PATEL NAGAR,
NEW DELHI - 110 008.

I, the undersigned, being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application*** *and* ***Complete Specification*** *filed in connection with Application for Patent No.* ***753/Del/02*** *dated* ***16th July 2002.***

Witness my hand this 10th Day of September 2003.

(S.K. PANGASA)
Assistant Controller of Patents & Designs

02 AUG 2002

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

753/DEL/02
16-7-02

(See Sections 5 (2), 7, 54 and 135 and rule 33A)

1. We, **RANBAXY LABORATORIES LIMITED,** a Company incorporated under the Companies Act, 1956 of 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"PROCESS FOR THE PREPARATION OF A DISPERSIBLE TABLET FOR ORAL ADMINISTRATION"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. SHASHIKANTH ISLOOR
b. SHISHIR BHAND
c. SUNILENDU BHUSHAN ROY
d. RAJIV MALIK

DUPLICATE

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. That we are the assignee or legal representatives of the true and first inventors.

5. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18,
Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana).
INDIA.
Tel. No. (91-124) 6343126, 6342001 – 10; 8912501-10
Fax No. (91-124) 6342027

6. Following declaration was given by the inventors in the convention country:

We, SHASHIKANTH ISLOOR, SHISHIR BHAND, SUNILENDU BHUSHAN ROY, RAJIV MALIK of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention in the convention country declare that the applicants herein, **Ranbaxy Laboratories Limited**, 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a. 

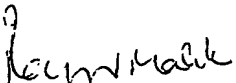
(SHASHIKANTH ISLOOR)

b. 

(SHISHIR BHAND)

c. 

(SUNILENDU BHUSHAN ROY)

d. 

(RAJIV MALIK)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

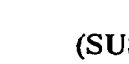
8. Followings are the attachment with the application:

a. Complete Specification (3 copies)
b. Drawings (3 copies)
c. Statement and Undertaking on FORM – 3
d. Fee Rs.5,000/- (Rupees Five Thousand only..) in cheque bearing No. **683127** dated **09.07.2002** on **ANZ Grindlays Bank, New Delhi.**

We request that a patent may be granted to us for the said invention.

Dated this **15TH** day of **July, 2002.**

For Ranbaxy Laboratories Limited



(SUSHIL KUMAR PATAWARI)
Company Secretary

FORM 2

0753-2

The Patents Act, 1970
(39 of 1970)

16 JUL 2002

COMPLETE SPECIFICATION
(See Section 10)

PROCESS FOR THE PREPARATION OF A DISPERSIBLE TABLET FOR ORAL ADMINISTRATION

DUPLICATE

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention relates to a process for the preparation of a dispersible tablet dosage form for oral administration comprising β-lactam antibiotics.

Beta-lactam antibiotics such as pencillins like amoxicillin, cephalosporins like cefalexin, cefpodoxime proxetil, cefuroxime axetil, cefaclor, carbapenems like loracarbef, imipenem etc. have a broad spectrum of antibacterial activity against many gram-positive and gram-negative microorganisms. The average daily dosage of these antibiotics is very high and the film coated tablets produced to deliver the daily dose are large and often inconvenient to swallow by the very young the elderly.

These dosage forms are also frequently not as bioavailable as the aqueous suspension formulation which exhibit the best bioavailability profile. Bioavailability of the drug is one critical parameter for determining the efficacy of pharmaceutical formulations. The medicine in a composition should be made available to the organism in as high an amount as possible and the optimum blood levels should be reached within the shortest possible time.

While the suspension dosage forms show the best bioavailability and can be easily administered to patients who have problems in swallowing, they have other drawbacks. They have to be reconstituted prior to administration and then stored under refrigerated conditions to prevent them from deterioration. Suspensions are also inconvenient to carry while traveling or when medication has to be taken away from home. They also entail the possibility of inaccurate measurement and dosing.

There is therefore a need of dosage forms which have all the advantages of a tablet or capsule formulation and the bioavailability and convenience of administration of a suspension. A dispersible tablet is one such dosage form which fills the void. They are easy to carry and can be reconstituted and administered to patients accurately and conveniently.

One of the key requirements of dispersible tablets is that they should disperse in an aqueous solution within a short time period of less than one minute to form a smooth suspension without any coarse lumps.

U.S. Patent No. 4,950,484 describes a dispersible tablet suited for amphoteric beta–lactam antibiotic which utilizes the combination of two different disintegrants: microcrystalline cellulose and low-substituted hydroxypropyl cellulose. The process for granulation as described in this

patent requires the use of 0-0.5 % of a wet binding agent. When we granulated amoxicillin as exemplified in example 3 of this patent, it resulted in extremely fragile granules with poor flow and compressibility characteristics. Such granules are not preferred for use on high speed compression machines used in commercial manufacture. The tablets fabricated using these granules had an unwet central mass when placed in still water even after one minute.

U.S. 5,955,107 assigned to FMC Corporation describes a pharmaceutical suspension tablet comprising a pharmacologically active ingredient, 1 to 6 percent croscarmellose sodium, 10 to 50 percent microcrystalline cellulose and 10 to 50 percent of co-processed additive consisting essentially of 75 to 95 percent microcrystalline cellulose and 5 to 25 percent of a calcium-sodium alginate complex.

U.S. Patent No. 5,837,292 assigned to Yamanouchi BV also describes fast, disintegrating and fast dissolving compositions containing a high amount of the drug containing a dispersing agent which is a water dispersible cellulose made by the chemical depolymerisation of highly purified wood pulp, the original crystalline areas of the fibers being combined with sodium carboxymethyl cellulose and spray dried (marketed under the trade name Avicel® RC 501).

US Patent Nos. 4,886,669 and 5,698,226 describe water dispersible tablet compositions containing swellable clays that generate high viscosity upon coming in contact with an aqueous solution. It has however been our experience that use of swellable clays delays the disintegration times of the tablet.

None of the prior art formulations therefore provide a simple, easy to manufacture formulation for dispersible tablets. Further, to ensure patient compliance the dispersible tablets should result in a suspension which has a smooth mouth feel without any gritty particles.

We have surprisingly found that it is possible to prepare dispersible tablet formulations using a simple formulation containing only one disintegrating agent used intragranularly and extragranularly without the use of specific combinations of disintegrants, gum etc as disclosed in the prior art.

It is an objective of the present invention to describe a process for the preparation of a water dispersible tablet formulation wherein the β-lactam antibiotic and an intragranular disintegrant incorporated either in the dry mix or in the granulating fluid, are aqueous granulated, the granules

are dried, mixed with extragranular disintegrant(s), fillers, flavours, sweeteners, lubricating agents and the resulting blend is then compressed to tablets.

It is another object of the present invention to describe a process for the preparation of a stable amoxicillin dispersible tablet formulation wherein the active and intragranular disintetrant incorporated either in the dry mix or the granulating fluid, are aqueous granulated, dried, mixed with extragranular disintegrants, fillers, flavours, lubricating agents, sweeteners and the resulting blend is compressed to tablets.

It is a further object of the present invention to describe a process for the preparation of a dispersible tablet formulation wherein the tablet when dispersed in an aqueous media, had a particle size distribution of d90 less than 600 μm.

The β-lactam antibiotics used in accordance with the present invention are selected from amongst penicillins like amoxicillin, cephalosporins like cefalexin, cefpodoxime proxetil, cefaclor cefuroxime axetil and carbapenems like loracarbef, imipenem etc. Most preferably, the β-lactam antibiotic is amoxicillin.

The particle size of amoxicillin used in accordance with the present invention was reduced to d90 less than 150 μm. More preferably the d90 was reduced to less than 75 μm as measured by Malvern laser diffraction method.

Amoxicillin is present at a concentration of 30-50 % w/w of the formulation. It is granulated with an aqueous solution of a disintegrant. The disintegrant is present intragranularly at a concentration of about 1 % about 2.5 % w/w of the tablet formulation.

The disintegrant used in accordance with the present invention was selected from amongst those belonging to the category of superdisintegrants such as croscarmellose sodium, sodium starch glycolate, polyvinylpyrrolidone and the like. Preferably, the disintegrant used was croscarmellose sodium.

The process of wet granulation is used for the preparation of dispersible tablets as it results in the formation of softer more porous granules which disintegrate in an aqueous solution to give a smooth suspension having no coarse lumps. Amoxicillin and similar drugs are however, known to be highly unstable when exposed to aqueous granulation. We have surprisingly found that not only

were the tablets prepared in accordance with our formulation stable upon storage, they also had excellent disintegration characteristics, hardness and low friability.

The granules obtained by the process of wet granulation are dried at a bed-temperature of less than 60°C to an equilibrium relative humidity of less than 40%. Preferably, the granules are dried at a bed temperature of 50°C to an equilibrium relative humidity of les than 25%. The drying temperature is critical as amoxicillin degrades at higher temperatures. The dispersible tablets thus made showed excellent stability even under accelerated stability conditions of 40°C / 75% RH.

The size of the particles in the suspension is very important for a smooth mouth-feel. As per the British Pharmacopoeia, all the particles of a suspension should pass through a 710 μm sieve without leaving any residue. A suspension complying to this requirement can, however, still have a gritty mouth-feel. It is preferable, therefore to have a finer suspension containing a more uniform size particles. The dispersible tablets made in accordance with the present invention forms a uniform dispersion upon swirling which has a smooth mouth feel and is free of gritty particles. The particle size distribution in the suspension was d90 less than 600 μm. Preferably, the d90 was less than 400 μm. The d50 was below 300 μm.

The granules thus prepared were mixed with an extragranular disintegrant, a filler, a sweetening agent, pharmaceutically acceptable flavours, coloring agents and lubricants.

The amoxicillin granules may optionally be mixed with clavulanic acid or its salts. Preferably, the clavulanic acid salt used in the formulation is potassium clavulanate. The ratio of amoxicillin to potassium clavulanate used in accordance with this invention is in the range from 12:1 to 1:1. Preferably the ratio is 7:1.

The extragranular filler is selected from amongst those commonly known in the art such as lactose and microcrystalline cellulose present at a concentration of between 40% to 70% w/w of the formulation. The extragranular disintegrant is selected from the group comprising croscarmellose sodium, sodium starch glycolate, polyvinyl pyrrolidone and the like. It is present at a concentration of between 1-5% w/w of the formulation.

The lubricants are selected from amongst those commonly known in the art such as colloidal silicon dioxide, talc, stearic acid, magnesium stearate and the like.

The following examples further exemplify the invention and are not intended to limit the scope of the invention.

TABLE 1

EXAMPLES 1-6

DESCRIPTION	EXAMPLES					
	1	2	3	4	5	6
Intragranular						
Loracarbef	--	--	--	--	--	205mg eq. to 200mg loracarbef
Amoxicillin (as trihydrate)	462.43	231.21	1010.80	693.12	231.0	--
Croscarmellose sodium	15.00	7.50	35.00	24.00	12.5	7.50
Colour (Allura Red A1 Lake)	0.50	0.25	0.50	0.34	0.50	0.25
Purified Water	qs	Qs	qs	qs	qs	qs
Extragranular						
Potassium clavulanate+MCC(1:1) eq to clav acid	-	-	-	-	71.90 28.5	--
Croscarmellose sodium	25.00	12.50	56.00	38.00	12.5	12.5
Flavour	10.00	10.00	20.00	20.00	20.0	10.0
Colour (Allura Red A1 Lake)	0.50	0.25	0.50	0.50	0.50	0.25
Colloidal silicon dioxide	10.00	5.0	21.00	15.00	5.0	5.0
Aspartane	10.00	10.00	20.00	20.00	10.0	10.0
Microcrystalline cellulose	451.57	215.79	1804.20	1227.88	200.0	215.79
Magnesium stearate	15.0	7.50	28.00	19.00	7.5	7.50
Total Tablet Weight	1000.00	500.00	2996.0	2058.00	600.00	500.00

Amoxicillin is granulated with an aqueous dispersion of croscarmellose sodium. The granules thus obtained are dried at a temperature of about 50-60°C. The equilibrium relative humidity (ERH) of the granules is NMT 40%. The dried granules are sized and blended with the remaining extragranular and compressed to tablets.

The dispersion prepared by suspending tablets made in accordance with example 1 of this invention was subjected to a particle size analysis as measured by a Malvern laser difractometer as given in Table 2.

TABLE 2

Particle size distribution of the suspension formed by dispersing a tablet made in accordance with example 1.

	Particle size in μm
d90	110.0
d50	37.0
d10	8.7

The fine particles present in the suspension were uniformly distributed and resulted in an opaque suspension with negligible transmitance when scanned in a UV spectrophotometer at 200-800 nm.

The 400mg dispersible tablet (made as per Example 1) was subjected to accelerated stability studies at 40°C / 75% RH as given in Table 3

TABLE 3

Period	Assay (mg)	Friability	Dissolution (%) in 90 minutes	Related Substances (% w/w)	
				Individual Impurities (NMT 1.0)	Total Impurities (NMT 4.0)
Initial	401.1	0.1	103.1	0.226	0.782
1 Month	399.0	0.2	101.9	0.168	0.963
2 Month	397.4	0.2	99.7	0.212	0.907
3 Month	397.2	0.2	100.7	0.150	1.002

As can be seen from the data given above the dispersible tablets made in accordance with the present invention displayed excellent stability characteristics under accelerated stability conditions of 40°C/75% even after 3 months.

A comparative, randomized two way crossover bioavailability study was conducted on our amoxicillin 400 mg dispersible tablet (as given in Example 1) formulation (test) and the commercially available Amoxil® (400 mg/5ml) suspension formulation (reference) in twenty four healthy male volunteers under fasting conditions and the 90 % confidence interval (T/R) and the ratio of least square means T/R (%) was calculated as given in Table 4.

TABLE 4

	Cmax (μg/ml)	AUC0-t (μg.h/ml)	AUC 0-α (μg.h/ml)
90% confidence interval (T/R)	85.3 – 94.1	93.7 – 98.8	93.9 – 99.0
T/R (%)	89.6	96.2	96.4

As can be seen from the data, the dispersible tablets have a bioavailability profile very similar to that of the suspension formulation and was within the bioequivalence limit requirements as stipulated by the USFDA.

WE CLAIM :

1. A process for the preparation of a water dispersible tablet formulation wherein the β-lactam antibiotic and an intragranular disintegrant, incorporated either in the dry mix or in the granulating fluid, are aqueous granulated, dried and mixed with extragranular disintegrants, fillers, flavours, sweeteners, lubricating agents, and the resulting blend iis then compressed to tablets.

2. A process as described in claim 1 wherein the β-lactam antibiotic is selected from amongst penicillins like amoxicillin, cephalosporins like cefuroxime axetil, cefpodoxime proxetil, cefalexin and carbapenams like loracarbef and imipenem.

3. A process as described in claim 1 wherein the β-lactam antibiotic is amoxicillin.

4. A process as described in claim 1 wherein the disintegrant is selected from amongst croscarmellose sodium, polyvinylpyrolidone, sodium starch glycolate and the like.

5. A process as described in claim 4 wherein the intragranular disintegrant is croscarmellose sodium.

6. A process as described in claim 4 wherein the disintegrant is present intragranularly at a concentration of about 1 % to about 2.5 % w/w of the tablet formulation.

7. A process as described in claim 4 wherein the extragranular disintegrant is croscarmellose sodium.

8. A process as described in claim 4 wherein the extragranular disintegrant is present at a concentration between 1-5% w/w of the formulation.

9. A process as described in claim 1 wherein the filler is selected from the group comprising lactose, microcrystalline cellulose, starch and the like.

10. A process as described in claim 9 wherein the filler is present at a concentration of between 40-70 % w/w.

11. A process as described in claim 1 wherein the lubricants are selected from amongst talc, magnesium stearate, stearic acid, colloidal silicon dioxide and the like.

12. A process as described in claim 1 wherein the dispersible tablet has a disintegration time of less than one minute.

13. A process as described in claim 1 wherein the suspension formed upon dispersion can completely pass through a 750 μm sieve.

14. A process for the preparation of a stable amoxicillin dispersible tablet formulation wherein the active and intragranular disintegrant, incorporated either in the dry mix or the granulating fluid, are aqueous granulated, dried, mixed with extragranular disintegrants, fillers, flavours, lubricating agents, sweeteners, and the resulting blend is compressed to tablets.

15. A process as described in claim 14 wherein amoxicillin comprises 30-50 % w/w of the formulation.

16. A process as described in claim 14 wherein amoxicillin has a particle size of d_{90} less than 150 μm.

17. A process as described in claim 14 wherein amoxicillin has a particle size of d_{90} less than 75 μm.

18. A process as described in claim 14 wherein the disintegrant is selected from amongst croscarmellose sodium, polyvinylpyrrolidone, sodium starch glycolate and the like.

19. A process as described in claim 18 wherein the intragranular disintegrant is croscarmellose sodium.

20. A process as described in claim 18 wherein the disintegrant is present intragranularly at a concentration of about 1 % to about 2.5 % w/w of the tablet formulation.

21. A process as described in claim 18 wherein the extragranular disintegrant is croscarmellose sodium.

22. A process as described in claim 18 wherein the extragranular disintegrant is present at a concentration between 1-5% w/w of the formulation.

23. A process as described in claim 14 wherein the filler is selected from the group comprising lactose, microcrystalline cellulose, starch and the like.

24. A process as described in claim 23 wherein the filler is present at a concentration of between 40-70 %.

25. A process as described in claim 14 wherein the lubricants are selected from amongst talc, magnesium stearate, stearic acid, colloidal silicon dioxide and the like.

26. A process as described in claim 14 wherein the granules are dried to an equilibrium relative humidity of less than at 40% at a bed temperature of not more than 60°C.

27. A process as described in claim 26 wherein the granules are preferably dried to an equilibrium relative humidity of less than 25% at a bed temperature of not more than 50°C.

28. A process as described in claim 14 wherein the dispersible tablet has a disintegration time of less than one minute.

29. A process as described in claim 14 wherein the suspension formed upon dispersion can completely pass through a 750 μm sieve.

30. A process as described in claim 14 wherein the amoxicillin granules may be further mixed with clavulanic acid or a salt thereof.

31. A process as described in claim 30 wherein the clavulanic acid salt is potassium clavulanate.

32. A process as described in claim 30 wherein the ratio of amoxicillin to potasium clavulanate is 12:1 to 1:1.

33. A process as described in claim 32 wherein the ratio of amoxicillin to potassium clavulanate is preferrably 7:1.

34. A process for the preparation of a water dispersible tablet formulation wherein the tablet when dispersed in an aqueous media, had a particle size distribution of d90 less than 600 μm.

35. A process as described in claim 34 wherein the d90 is less than 400 μm.

36. A process as described in claim 34 wherein the d50 is less than 300 μm.

37. A process for the preparation of a stable, dispersible tablet formulation of amoxicillin wherein the tablet is bioequivalent to the amoxicillin suspension formulation available commercially under the trade name Amoxil™ as required by the USFDA.

38. A process as described and exemplified herein.

Dated this **16TH day of July, 2002.**

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary